

# Serum Cholinesterase and Euglobulin Lysis Time in Chronic Cor Pulmonale

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Frank myocardial infarction is very seldom encountered in patients with chronic cor pulmonale. Among the 179 patients with myocardial infarction admitted to our clinic between 1956 and 1965 there were none with chronic cor pulmonale. However, anatomo-pathological data show that atherosclerotic changes in the aorta are not less frequent in subjects with cor pulmonale than in control subjects of the same age (Rub, Fekete, and Ionescu, 1967). In addition, among 303 patients with decompensated chronic cor pulmonale admitted to our clinic over a period of five years, there were none with a peripheral thrombophlebitis. However, this does not exclude the occurrence of thromboembolic episodes in the pulmonary vessels of patients with chronic cor pulmonale. Indeed it has been suggested that thrombosis of pulmonary vessels could be a cause of the cor pulmonale (Dexter, 1965). Changes in platelets and coagulability in cor pulmonale have been previously reported (Beltrami and Bucher, 1966; Bouvier and Korálnik, 1962; Donner, 1959). We therefore decided to investigate plasma fibrinogen and fibrinolytic activity in this disorder.

An impairment in the production of serum proteins and lipoproteins, including factors involved in coagulation and fibrinolysis, is to be expected in chronic cor pulmonale, when the liver is affected by congestive heart failure. Estimation of the hepatic involvement in this condition is a difficult task, since liver function tests in cardiac patients are influenced by extrahepatic factors. It has been found, however, that serum cholinesterase is a reliable indicator of the proteosynthetic function of the liver (Hall and Lukas, 1937; Antopol, Schiffrin, and Tuchman, 1938; Cucuianu, Mureşan, and Mureşan, 1966), and is not directly influenced by extrahepatic factors or haemodynamic changes (Hărăguş *et al.*, 1966).

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## SUBJECTS AND METHODS

In a preliminary study (Hărăguş *et al.*, 1966) serum cholinesterase was investigated in patients with chronic cor pulmonale and heart failure: 28 patients with coronary heart disease with congestive heart failure, and 32 patients with rheumatic valvular disease and right-sided heart failure.

Serum cholinesterase, serum cholesterol, plasma fibrinogen, and fibrinolytic activity were subsequently investigated in the following groups of patients.

*Group A* included 30 healthy young subjects without first-degree relatives affected by atherosclerosis.

*Group B* was composed of 30 atherosclerotic patients (14 men, 16 women) between 52 and 78 years, without heart failure, most of them survivors of myocardial infarction.

*Group C* included 17 patients (12 men, 5 women) between 25 and 68 years (mean 54 years) with chronic cor pulmonale and heart failure, selected according to W.H.O. criteria (1961), namely: (a) presence of a chronic disease of lungs likely to produce chronic cor pulmonale; (b) signs of hypertension in the pulmonary arteries; (c) right ventricular hypertrophy. All these patients had hepatic enlargement. The jugular venous pressure was not measured. This group contained only "pure" cases of chronic cor pulmonale without coronary heart disease. It should be remembered that congestive heart failure in a patient with chronic disease of the lungs is not always due to pulmonary disease, and could be due to associated atherosclerotic coronary artery disease, though frank myocardial infarction is uncommon.

Therefore, a further group was studied, *Group D*, containing 14 patients (10 men, 4 women) between 42 and 80 years (mean 57 years) with decompensated chronic cor pulmonale, complicated by coronary heart disease or generalized atherosclerosis, and presenting one or several of the following characteristics: first degree relatives affected by coronary heart disease; arterial hypertension; diabetes mellitus; atrial fibrillation or angina pectoris on exertion. The presence of coronary heart disease in these cases could be strongly inferred. Nine patients were found to have enlargement of the liver.

TABLE

SERUM CHOLINESTERASE, SERUM CHOLESTEROL, PLASMA FIBRINOGEN, EUGLOBULIN LYSIS TIME, AND THE RATIO PLASMA FIBRINOGEN/EUGLOBULIN LYSIS TIME IN YOUNG HEALTHY CONTROLS (A), ATHEROSCLEROTIC PATIENTS WITHOUT HEART FAILURE (B), AND PATIENTS WITH HEART FAILURE DUE TO "PURE" COR PULMONALE (C) OR CHRONIC COR PULMONALE COMPLICATED BY CHRONIC ISCHAEMIC HEART DISEASE (D)

Group		A	B	C	D	Statistical significance (p)
No. of observations		20	30	17	17	
Serum cholinesterase ( $\mu$ mole/ml. per hr.)	Mean	227	280	139	168	A vs B < 0.01 A vs C < 0.001 A vs D < 0.001 B vs C < 0.001 B vs D < 0.001 C vs D > 0.1
	SE	$\pm 9$	$\pm 14$	$\pm 17$	$\pm 20$	
Serum cholesterol (mg./100 ml.)	Mean	163*	230	165	197	A vs B < 0.001 A vs C > 0.1 A vs D < 0.05 B vs C < 0.001 B vs D < 0.05 C vs D < 0.05
	SE	$\pm 4$	$\pm 8$	$\pm 6$	$\pm 12$	
Plasma fibrinogen (mg./100 ml.)	Mean	283	503	533	731	A vs B < 0.001 A vs C < 0.001 A vs D < 0.001 B vs C > 0.1 B vs D < 0.05 C vs D < 0.05
	SE	$\pm 12$	$\pm 31$	$\pm 46$	$\pm 73$	
Euglobulin lysis time (min.)	Mean	285	612	185	460	A vs B < 0.001 A vs C < 0.001 A vs D < 0.02 B vs C < 0.001 B vs D < 0.05 C vs D < 0.01
	SE	$\pm 17$	$\pm 28$	$\pm 22$	$\pm 65$	
Plasma fibrinogen/euglobulin lysis time	Mean	1	0.8	4	1.9	A vs B < 0.02 A vs C < 0.001 A vs D < 0.05 B vs C < 0.001 B vs D < 0.02 C vs D < 0.01
	SE	$\pm 0.06$	$\pm 0.05$	$\pm 0.6$	$\pm 0.4$	

\* It should be mentioned here that mean values of serum cholesterol were found to be lower in the Rumanian population than those generally reported in Anglo-Saxon or Scandinavian reports.

Serum cholinesterase was measured according to the photocolorimetric method of De la Hueraga, Yesnick, and Popper, as described by Augustinsson (1957), and the results were given in  $\mu$ mole/ml. per hour. Serum cholesterol was measured according to Zlatkis, Zak, and Boyle (1953), and fibrinolytic activity was estimated from the euglobulin lysis time (Von Kaulla, 1963). Fibrinogen was assayed photocolorimetrically by its tyrosine content (Ratnoff and Menzie, 1951).

### RESULTS

In patients with heart failure due to chronic cor pulmonale, the reduction in serum cholinesterase was significantly greater than in those patients with heart failure of different aetiology but similar duration. A progressive reduction in serum cholinesterase was noted in patients with chronic cor pulmonale followed over a longer period of time, as heart failure became irreversible.

Necropsy in 4 patients with decompensated chronic cor pulmonale revealed changes suggesting a chronic hepatitis in one; the only histological changes in the other 3 were those of chronic passive congestion.

As shown in the Table and Fig. 2, euglobulin lysis time was found to be significantly shorter in patients with "pure" chronic cor pulmonale than in the other three groups. As the plasma fibrinogen level was higher in control subjects, a striking increase in the ratio of plasma fibrinogen to euglobulin lysis time was noted in patients with "pure" chronic cor pulmonale.

### DISCUSSION

The reduction in serum pseudocholinesterase in patients with chronic cor pulmonale is a result of congestive heart failure giving rise to an impairment of the proteosynthetic function of the liver. Though mean values of serum pseudocholinesterase in patients with coronary heart disease and congestive heart failure were below normal mean values (Fig. 1), we have found that in certain cases the enzymatic activity may be normal or even increased. This could be explained by the fact that pseudocholinesterase activity is increased in obese (Berry, Cowin, and Davies, 1954) and hyperlipaemic subjects (Cucuianu, Popescu, and Hărăguș, 1968), and that mean values of pseudocholin-

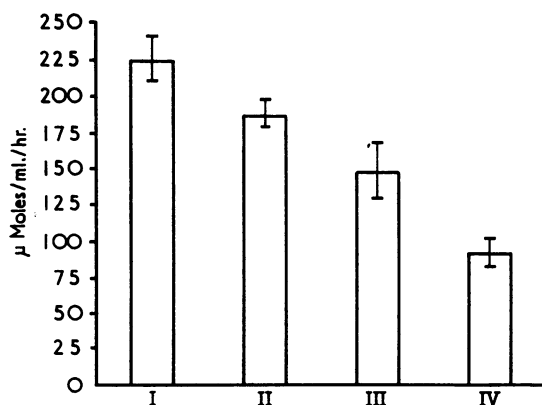


FIG. 1.—Serum cholinesterase ( $\mu$ mole/ml. per hour) in healthy controls (I) and in patients with advanced congestive heart failure due to coronary heart disease (II), rheumatic valvular disease (III), and chronic cor pulmonale (IV).

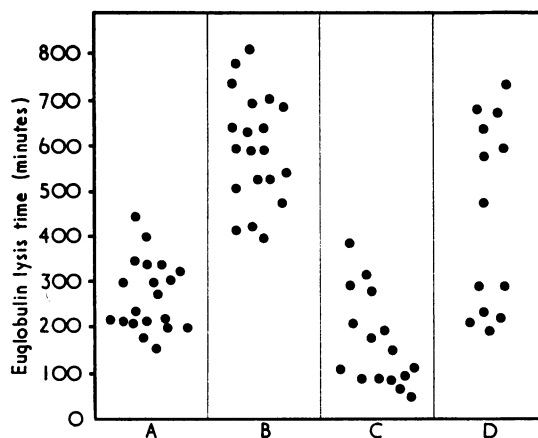


FIG. 2.—Euglobulin lysis time (min.) (A) in control subjects, (B) atherosclerotic patients, (C) "pure" chronic cor pulmonale, and (D) chronic cor pulmonale complicated by coronary heart disease

esterase are higher in atherosclerotic patients, without heart failure, than in normal controls (see the Table). Consequently, the lower serum pseudocholinesterase in congestive heart failure due to coronary heart disease proceeds from a higher initial level.

As the proteosynthetic function of the liver was found to be impaired in chronic cor pulmonale, a decreased level of plasma fibrinogen was to be expected. It was found, however, that plasma fibrinogen values were high in both "pure" chronic cor pulmonale and in cor pulmonale complicated by coronary heart disease. It seems that the role played by the liver in the production of fibrinogen is less important than its role in the synthesis of serum cholinesterase. In fact a decrease in plasma fibrinogen is seldom encountered, even in cases of advanced cirrhosis of the liver (Kupfer *et al.*, 1964). A higher level of plasma fibrinogen was found even in patients without inflammatory changes of the lungs, a fact that we cannot explain. The increased fibrinogen was in contrast to the low erythrocyte sedimentation rate often found in chronic cor pulmonale. As a rule, the erythrocyte sedimentation rate increases when plasma fibrinogen level becomes higher (Wuhrmann and Märki, 1963), but this does not happen, however, in chronic cor pulmonale, probably because of the simultaneous polycythaemia and acidosis, with swollen erythrocytes delaying sedimentation.

Though euglobulin lysis time largely depends on the level of plasma fibrinogen (Donner, 1963; Cucuianu *et al.*, 1966), a short lysis time was emphasized in the group of patients with "pure" chronic cor pulmonale.

Acute hypoxia is known to activate fibrinolysis transiently (Kwaan, Lo, and McFadzean, 1956; Kowarzyk *et al.*, 1962; Von Kaulla, 1963). However, these observations are not sufficient to explain the long-standing acceleration of fibrinolysis in chronic cor pulmonale. Enhanced fibrinolysis is not a common finding in cases of anaemia with hypoxia, though it has been noted sometimes (Révol *et al.*, 1958).

Activation of fibrinolysis frequently occurs in cirrhotic patients (Ratnoff, 1949; Révol *et al.*, 1958), perhaps because of a decreased production of inhibitors of fibrinolysis (Dorca *et al.*, 1960; O'Connell, Grossi, and Rousselot, 1964) or because of deficient clearance of the activators in the liver (Fletcher *et al.*, 1964).

It is possible that impaired hepatic function and hypoxia could together accelerate fibrinolysis in chronic cor pulmonale. This activation contrasts with the delayed clot lysis in coronary heart disease, fibrinolytic insufficiency in coronary heart disease being well known (Moga *et al.*, 1960).

A decrease in the number of platelets (Beltrami and Bucher, 1966), deficient clot retraction (Bouvier and Korálnik, 1962), and deficient thromboplastin generation (Donner, 1959) have also been found in heart failure due to chronic cor pulmonale. These data and our findings might furnish a humoral explanation for the low incidence of thrombotic episodes in this anomaly. The protection against myocardial infarction might be explained also by the development of collateral vessels as a result of prolonged hypoxia (Nonkin, Dick, and Baum, 1964).

Though frank myocardial infarction was rarely

seen in our patients with chronic cor pulmonale, the development of atherosclerosis was apparently not inhibited. This was shown by the existence of cor pulmonale complicated by coronary heart disease, and by anatomic-pathological data which demonstrated that atherosclerotic changes of the aorta were not less frequent in chronic cor pulmonale than in control subjects of the same age (Rub *et al.*, 1967).

#### SUMMARY

A decrease of serum cholinesterase was noted in patients with heart failure. This impairment of the proteosynthetic function of the liver was greater in patients with chronic cor pulmonale than in those with heart failure of other aetiology.

An accelerated euglobulin lysis time was also noted in patients with heart failure due to chronic cor pulmonale uncomplicated by coronary heart disease. Activation of fibrinolysis was considered to be an effect of both hypoxia and liver insufficiency. These humoral changes might explain why heart failure due to chronic cor pulmonale is so rarely accompanied by thrombotic events.

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